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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/242,657	02/19/99	JENSEN	P 55411.000002

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	7

DATE MAILED: 03/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/242,657	Jensen, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1 & 2*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

2. Claim 16 is objected to because of the following informalities: the use of parentheses around the phrase "..promoter library.." is confusing in that it is unclear whether the phrase is meant to simply clarify the phrase "a set of promoters" or meant as a further limitation on the body of the claim. Similarly, the parentheses around the phrase "a spacer sequence" in claim 16 are also confusing. It would be remedial to replace the parentheses in each case with commas, or to simply drop the phrases entirely since they do not add anything substantial to the claim.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the term "library" are unclear. The specification does not appear to define a promoter library with regard to the number of members required before a set of promoters can be considered a library. Although claim 1 does have the functional language of "..the promoter library spanning, with respect to promoter activitities for said gene, a range of interest, in small steps, each step preferably changing the activity by 50-100%", the metes and bounds of the phrase "..range of interest.." are unclear. This term also does not appear to be well defined within the text of the specification. What criteria determine a "range of interest"? Is it a range between 20 and 50% of maximal expression for a desired gene? Is it the range from no detectable expression of a gene of interest to maximal expression and accumulation of the gene product as insoluble aggregates? In the absence of a defined number of promoter sequences, and in the absence of a defined "range of interest", it is difficult to determine whether a given set of promoters meeting the other limitations of claim 1 (e.g. with regard to having at least half of each of the consensus sequences maintained in each member of the library and having variable sequences in the spacer regions flanking the consensus sequences) actually falls within the scope of claim 1 as a library. It would be remedial to amend the claim to clearly indicate what constitutes a "range of interest".

Claims 1 and 16 are vague and indefinite in that the metes and bounds of the term "consensus sequences" are unclear. The term does not appear to be well defined in the specification and is not well defined in the art. One inventor's consensus sequence is likely to be another inventor's non-conserved sequence. It is unclear as the claim is written as to which

sequence the two "consensus" sequences are in agreement with and to what degree they are required to be in agreement. Does the term "consensus" mean simply that the two "consensus" sequences share homology with the identified promoter, or does it mean that they share homology with a conserved sequence or sequences in a promoter sequence that is conserved throughout an organism's genome? Upon reading the specification, it appears the latter definition is intended by applicants. How well conserved across a number of different promoters does a sequence have to be in order to be considered a consensus sequence? Does it have to be 100% identity? Would 75% identity be sufficient? How many different promoter sequences would have to be considered in order to determine a consensus sequence for a given class of promoter? Would a comparison of two promoters identified in an organism showing 100% identity at -10 and -35 regions satisfy the definition of a consensus sequence? It would be remedial to amend the claim language in claims 1 and 16 to clearly indicate what is intended by the term "consensus sequences".

Claim 1 is also vague and indefinite in that the metes and bounds of the phrase "...at least half of each of said consensus sequences is kept constant in all of the individual promoter sequences and...." are unclear. Does this phrase mean that 50% of each consensus sequence is conserved in each of the members of the promoter library, but that any permutation of the consensus sequence having 50% identity with the consensus sequence is acceptable? Or does this phrase mean that 50% of the consensus sequence is absolutely conserved among each member of the promoter library (e.g. GGGatc, GGGtag, GGGctc.....), and thus greatly reducing

the number of possible members of the promoter library. It would be remedial to amend the claim language to clearly indicate which possibility is encompassed by the indicated phrase.

Claim 1 is also vague and indefinite in that the metes and bounds of the phrase "..is varied to comprise nucleotides that are selected randomly among the nucleobases A, T, C and G." are unclear. Does this phrase specify that each possible nucleotide must be represented at each possible position in the spacer region for a set of promoters to satisfy the limitation of being a library according to claim 1? Or does it simply mean that the library was constructed in such a way as to allow essentially random incorporation of nucleotides into the spacer sequence and that every possible permutation need not be present? It would be remedial to clearly indicate what is intended by the phrase "..is varied to comprise nucleotides that are selected randomly among the nucleobases A, T, C and G." with regard to the requirements for representation of each of the nucleotides at each possible position within the spacer sequence.

Claims 1 and 17 are also vague and indefinite in that the use of the term "preferably" with regard to a claim limitation is inherently indefinite, making it unclear as to whether the limitation that follows the term is actually part of the claim limitation. The term "preferably" implies that what follows is an optional limitation. In which case, if the limitation of 50-100% difference in activity per step is not binding, the limitation of "small steps" is not defined and is a relative limitation having little meaning. Would a jump of 200% activity from one step to another constitute a "small step"? It would be remedial to amend the claims by dropping the term from the claim language.

Claim 2 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "spacer sequence(s)" in claim 1, upon which claim 2 is dependent. Claim 1 appears to specify only one spacer sequence per member of the library, while the use of the term "spacer sequence(s) in claim 2 implies that more than one spacer can be found in a member of the promoter library of claim 1.

Claim 4 is vague and indefinite in that the phrase "..at least one recognition site for restriction endonuclease" is grammatically incorrect because it lacks a period at the end of the claim and a definite article before the term "restriction nuclease".

Claims 5 and 12 are vague and indefinite in that they contain a large Markush group that should be recited in appropriate Markush language. It would be remedial to amend claim 5 to read "..the selected organism or group of organisms is selected from the group consisting of prokaryotic organisms.". Similarly, it would be remedial to amend claim 12 to read "..the selected organism or group of organisms is selected from the group consisting of eukaryotic organisms.

Claim 8 is vague and indefinite in that the metes and bounds of the term "conserved motifs" are unclear. What exactly constitutes a conserved motif in the context of this claim? What sort of motif is being claimed (e.g. a restriction site, a transcription factor binding site, a stem-loop of undefined structure, etc.)? With what sequences is it being compared in order for it to be a considered conserved motif? How much identity between this and the base sequence is

required before it is considered to be "conserved"? It would be remedial to amend the claim language to clearly indicate what is intended by the term "conserved motif".

Claims 11 and 14 are vague and indefinite in that the metes and bounds of the term "minor variations hereof" are unclear. The term "thereof" is misspelled in the claim. Also, what exactly constitutes a "minor variation" of the base sequence? Would a variation of 3 of 10 nucleotides constitute a "minor" variation? It would be remedial to amend the claim to clearly indicate what is meant by the term "minor variation", or to simply drop the term from the claim.

Claims 18 and 21 are vague and indefinite in that the metes and bounds of the phrase "..(ii) cloning said set of promoters into the organism placing in each clone the gene to be expressed under the control of at least one promoter of the set." are unclear. Does the term "clone" refer to the promoter/gene combination or to the organism transformed with the promoter/gene construct? Does the phrase mean that the entire set of promoters is cloned into one organism (e.g. a pig) or into an organism as a species (e.g. into E.coli)? It would be remedial to amend the claim language to clearly indicate whether the entire library of promoter/gene constructs is transformed into a single organism, or whether it is transformed into many organisms.

Similarly, claims 18 and 21 are vague and indefinite in that the metes and bounds of the phrase "..(iii) cultivating the clones and selecting a clone showing optimised flux of gene product formation....." are unclear. Again, does the term "clone" refer to the promoter/gene construct, or to the organism transformed with the promoter/gene construct? Also, what exactly is meant by

the term "optimized flux of gene product formation"? Does this mean the maximum level of gene product formation? Does it mean the maximum level of gene product formation in an active, soluble form, as opposed to even greater amounts obtained in an insoluble form? Does it mean a sub-maximal level of gene product formation in order to achieve a physiologically acceptable level of gene product activity for some experimental purpose? Upon reading the specification it appears applicants mean to specify that the clone showing optimal levels of gene expression for the gene of interest such that maximum levels of gene product accumulate in the cell should be selected. It would be remedial to amend the claim to clearly indicate what is meant by the phrase "optimized flux of gene product formation.".

Claim 22 is vague and indefinite in that the terms "is capable of" and "is obtainable" are inherently vague and indefinite unless the conditions for "capability" or "obtainability" are clearly specified.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5-8, 10 and 22 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Nilsson et al (AD).

Nilsson et al teach the comparison of a set of tRNA and rRNA promoter sequences (i.e. a promoter library) isolated from *L.lactis* and *L.cremoris* (Fig 2). The different promoter sequences all feature 100% identity at ~-44 (AGTT) and at ~-15 (TG), as well as strong identity at -35 and -10 (Fig 2). Read one way, the sequences at -35 and -10 satisfy the limitation of claim 1 that at least half of each of the consensus sequences are kept constant in all of the individual promoter sequences (i.e. at least 50% identity is maintained at each consensus sequence, but the same nucleotides within the consensus sequences are not absolutely maintained across all of the sequences). The -44 and -15 sequences satisfy this limitation in either interpretation. Outside of these regions of strong identity there is far less identity and far more variability among the different members of the "library", where presumably an A, T, C or G could have been inserted barring any structural/functional limitation. There does not appear to be a limitation in either the claim language of claim 1 or in the specification that the different nucleotidase must be present in a 1:1:1:1 ratio at each nucleotide position in the spacer regions across the members of the promoter library. The different promoter sequences taught by Nilsson et al are extremely unlikely to all have the same strength of promoter activity for a given gene sequence under their control. Given the use of the term "preferably" in claim 1 with regard to defining the relative term "small steps", there is in essence no limitation in claim 1 regarding differences in promoter activity among the members of the library, so long as there are differences (i.e. an activity "range

of interest"). Finally, any of the promoters taught by Nilsson et al in Figure 2 are "capable of" optimal expression of a gene and are "obtainable by the method of claim 21". One could argue that the promoter sequences listed in Figure 2 are already optimized for expression of the tRNA and rRNA sequences they are associated with in the organisms from which they were isolated. Any one of the sequences in Figure 2 would reasonably be expected to be produced by practicing the method of claim 21 on any one of the other sequences taught in Figure 2 by Nilsson et al.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 8:00 AM to about

4:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GGL

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

TERRY MCKELVEY
PRIMARY EXAMINER

March 26, 2000